REMARKS

Status of the Claims

Claims 1-5 were pending in this application prior to entry of the present amendments.

Claims 3-5 were withdrawn from consideration

Claims 3-5 are canceled herein without prejudice or disclaimer.

Claims 1 and 2 are amended herein.

Claims 6-10 are newly added.

No new matter is introduced by the present amendments and newly added claims. Applicants reserve the right to present any withdrawn or canceled subject matter in one or more continuation or divisional applications.

Objections

The Specification has been amended in view of the Examiner's objection to include sequence identifiers where appropriate. In addition, the claims are amended as to the formalities objected to by the Examiner.

The Examiner considers claim 5 a method claim to a method of a sandwich immunoassay, which is classified in Group II of the restriction requirement of March 8, 2007. In view of the finality of the restriction, claims 3, 4 and 5 have been canceled and new claims 8-11 have been directed to an immunoassay product. These claims are supported on pages 9 and 11 and Examples 7-9 of the specification.

The Examiner objects to the previously filed declaration. Applicants will provide the Office with a new declaration in short order and respectfully request that this objection be held in abeyance.

Applicants understand that the Examiner has not reviewed non-English language references F1-F5 submitted with the IDS of November 28, 2000. Applicants submit herewith a supplemental information disclosure statement citing the English language abstracts of these documents for the Examiner's review.

Claim rejections

35 U.S.C. §112, ¶ 1

Claims 1 and 2 stand rejected as lacking enablement under 35 U.S.C. §112, first paragraph. Specifically, the Examiner contends that "it is not clear whether the '30-most N-terminal amino acids of human PIIINP' would include the signal peptide" and further that "because different laboratories may have different number of the same protein" recitation of the amino acid position without a SEQ ID NO is not enabling. Applicants traverse this rejection.

The antibodies provided in the specification bind to the 30-most N-terminal amino acids of the Col1 region, as shown in Figure 2. SEQ ID NO:2 is the full length protein, including the prepro-peptide sequence that is cleaved off during processing of the molecule. As shown in Figure 1, as well as in Table 2, the amino acid sequence to which the antibodies are reactive begins at amino acid 25 of SEQ ID NO:2. This is described in detail in Example 1 (see specifically page 124, lines 1-19), which identifies primer P3 as the amino terminal primer. The sequence is identified in bold in table 2 (Gln, Glu, etc.) and in Figure 1 below primer P3 (Gln, Glu, etc.). This sequence goes to the sequence identified by primer P11-2, identified in Figure 1. The full sequence is thus Gln-Glu-Ala-Val-Glu-Gly-Gly-Cys-Ser-His-Leu-Gly-Gln-Ser-Tyr-Ala-Asp-Arg-Asp-Val-Trp-Lys-Pro-Glu-Pro-Cys-Gln-Ile-Cys-Val. Accordingly, Applicants submit that the identity of the "30-most N-terminal amino acids of human PIIINP" is abundantly clear from the specification.

Nevertheless, solely to advance prosecution of this case, claim 1 is amended herein to recite an antibody that recognizes an "epitope within the 30 most N-terminal amino acids of the Col1 domain of human PIIINP, wherein the sequence of the 30 most N-terminal amino acids is Gln-Glu-Ala-Val-Glu-Gly-Gly-Cys-Ser-His-Leu-Gly-Gln-Ser-Tyr-Ala-Asp-Arg-Asp-Val-Trp-Lys-Pro-Glu-Pro-Cys-Gln-Ile-Cys-Val." This amendment is supported in Example 1, Table 2, and Figures 1 and 2 of the Specification, as discussed above. Applicants believe this amendment overcomes the rejection.

35 U.S.C. §102(b) over Lotterer

The Examiner has rejected claims 1 and 2 under 35 U.S.C. §102(b) as anticipated by Lotterer, et al. (1993) "A New Test for the Determination of Aminoterminal Procollagen-III-Peptide in Serum Using Monoclonal Antibodies," Abst. T-254. The Examiner contends that the

product used in the reference is the same as the claimed product and alleges that the binding to the 30 most amino acids of PIIINP, trimeric PIIINP or subsequence from the col2 domain of PIIINP are inherent properties. Applicants traverse this rejection on the ground that the antibodies of Lotterer are not the same as the instantly claimed monoclonal antibodies and, in any event, the Examiner has provided no technical rationale to support the conclusion that Lotterer's antibodies inherently possess the claimed features.

For a prior art reference to inherently anticipate an invention, the Examiner must provide a rationale or evidence tending to show inherency. See MPEP § 2112; "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

Lotterer is silent as to the epitopes recognized by the monoclonal antibody, or even as to how many species of PIIINP were recognized by the antibody. As noted in the specification, the nature of the epitope recognized by the monoclonal antibodies commercially available at the time of the Lotterer studies was not known. What was known about these antibodies is that they recognize epitopes **not** located in the Col1 region and that they recognize multiple PIIINP species in human body fluids (see pages 5 and 7 of the specification). The Examiner has presented no evidence or scientific rationale that reasonably show that the antibody described in Lotterer specifically recognized the 30 N-terminal amino acids of PIIINP, as recited in the pending claims. In fact, there is no evidence at all that the Lotterer antibody recognized this portion of the protein. There is no suggestion anywhere in Lotterer that would indicate to one of skill in the art that this antibody differed in any way from the available antibodies described at length in the background of the present specification.

In contrast to the antibodies available at the time of Lotterer, the antibodies recited in the present claims **specifically recognize** the "30 most N-terminal amino acids" of PIIINP. The claimed antibodies are an improvement over prior antibodies that recognize other epitopes of PIIINP. The claimed antibodies allow more specific differentiation between collagen synthesis versus collagen breakdown (as described, for example, on page 22 of the specification). As shown in Examples 7 and 8, the antibodies directed at the specific N-terminal portion of the

PIIINP molecule exclusively recognize higher weight species of PIIINP that show the *de novo* deposition of the molecule and preferentially bind trimeric PIIINP. Being able to appropriately distinguish synthesis versus breakdown products is of critical importance in the diagnosis of various liver disorders (see Specification, page 3).

Accordingly, Applicants respectfully submit that there is no reasonable basis for concluding that the antibodies of Lotterer specifically recognize the "30 most N-terminal amino acids" of PIIINP, in view of the fact that the antibodies know in the art at the time of Lotterer recognized epitopes which are not located in the Col1 region and also recognize multiple PIIINP species in human body fluids. For at least these reasons, Applicants submit that the rejection over Lotterer is deficient and should be withdrawn.

35 U.S.C. §102(b) over Xie

The Examiner has rejected claims 1-2 under 35 U.S.C. §102(b) as anticipated by Xie, et al. (1994) *Mianyixue Zazhi* 10(1):56-8, abstract. The Examiner contends that this reference describes the same antibody as that claimed, and that recognition of the 30-most N-terminal amino acids is an inherent property of the described antibody. Applicants traverse this rejection.

Xie et al. describe the production of antibodies to the propeptide of PIIINP. The antibodies were designed to localize pre-procollagen in certain cell types. As the Examiner is aware, the pre-procollagen molecule includes a signal sequence which is not present in procollagen. As depicted in Figure 2 of the present application, and recited in the amended claims, Applicants' antibodies specifically recognize the first 30 N-terminal amino acids of procollagen **not** including the signal sequence. Therefore, the antibodies described in Xie are clearly not the antibodies presently claimed. Applicants submit that there is simply no basis for the assertion that the antibodies of Xie would inherently possess the claimed characteristics. Reconsideration and withdraw of this rejection is requested.

35 U.S.C. §103(a)

The Examiner has also rejected claims 1-2 under 35 U.S.C. §103(a) as obvious in view of Brocks et al. (1993) *Matrix* 13:381-7 in view of U.S. Patent No. 5,512,283 (as evidenced by GenBank Accession No. P02461). Briefly, The Examiner asserts that Brocks uses epitope scanning to determine epitopes recognized by an antiserum, certain of which represented bovine

amino acid sequences identical to certain amino acids of the first 30 N-terminal amino acids of human PIIINP. The Examiner contends that, because binding to the Brocks epitopes was weak, it would have been obvious to use the methods described in the '283 patent to produce a monoclonal antibody against the eptiopes of procollagen taught by Brocks.

As noted throughout the specification, it has historically been exceedingly difficult to provide antibodies against collagen molecules, particularly collagen III, that specifically recognize the human protein. This is apparent from the extensive description of the prior art that shows that numerous investigators had, for several decades, tried to provide such molecules. These were directed against various portions of the molecule. However, until the present invention, it was not clear that an antibody that could recognize the 30 most N-terminal amino acids of the PIIINP would be useful for such specific recognition, and would be able to differentiate between collagen breakdown and collagen synthesis. An antibody described in the present specification and recited in the amended claims is now used in a commercially available Enhanced Liver Fibrosis test, the first CE-marked, standardized non-invasive blood test for assessing the status of liver fibrosis in a patient.

Applicants note that Brocks describes the production of polyclonal antibodies against a synthetic peptide representing the *14 C-terminal amino acids of the N-terminal propeptide* of rat and bovine procollagen type III. The goal in Brocks was to identify antibodies that **did not** react with the Col1 domain. As noted in Brocks, "this antigenic domain is not present in the Col1 antigen" (page 382, left column, second paragraph). There is no teaching or suggestion in Brocks that an antigen of interest would be the 30-most N-terminal amino acids of the human protein.

In contrast, the presently claimed antibodies specifically recognize the 30 most *N-terminal amino acids of the human protein*. The disclosure of antibody generation in Brocks is directed at both an entirely different species and an entirely different molecular entity. Even if one of skill in the art would have chosen to produce monoclonal antibodies based on the peptide sequence in Brocks, it would have been a different antibody.

Furthermore, as noted in Brocks, human antigen was non-reactive against the antibody generated (see abst.). One of skill in the art would not have been motivated to make any further antibodies based on the disclosure in Brocks for the purpose of using it against human antigens,

as the disclosed antibody was **not** reactive with human proteins. Thus, there would be no motivation to use any peptide sequences disclosed in Brocks to produce a monoclonal antibody by the methods described in the '283 patent. Furthermore, as the antibody of Brocks did not recognize the human protein, there is no reason that one of skill in the art would expect any antibody produced using this sequence to specifically recognize the 30-most N-terminal amino acids of the human Col1 domain, as recited in the amended claims. Therefore, the references cited, alone or in combination, do not suggest the production of an antibody directed against the 30 most N-terminal amino acids of the Col1 region, as recited in the amended claims. Accordingly, Applicants submit that the present claims fully distinguish over Brocks and the '283 patent, whether taken alone or in combination. Withdrawal of this rejection is requested.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendments and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

AUTHORIZATION

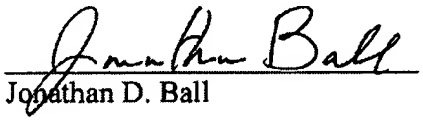
The Commissioner is hereby authorized to charge any fees which may be required for this amendment, or credit any overpayment to Deposit Account No. **50-3732**, Order No. **14173.105005**. Furthermore, in the event that an extension of time is required, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to the above-noted Deposit Account No. **50-3732** and Order No. **14173.105005**.

Respectfully submitted,

KING & SPALDING, L.L.P.

Dated: August 31, 2007

By:



Jonathan D. Ball

Registration No. 59,928

Mailing Address:

KING & SPALDING, L.L.P.
1185 Avenue of the Americas
New York, New York 10036-4003
(212) 556-2115
(212) 556-2222 (Fax)